

REMARKS/ARGUMENTS

This Amendment and Remarks are in response to the Final Office Action dated October 29, 2007. Reconsideration of this application and entry of this Amendment after Final are respectfully requested. This response is submitted with a Request for Continued Examination. The proposed amendment places the claims in better form for appeal. Additionally, this amendment addresses items brought up by the Examiner in the Final Office Action and in the Interview of March 4, 2008. In view of the amendments and following remarks, favorable consideration and allowance of the application is respectfully requested.

Applicants thank Examiners Sharon Hurt and Bruce Campbell for the Telephonic Interview with Applicant's representatives on March 4, 2008. As discussed during the Interview, Applicants are submitting the arguments presented in the interview and a declaration by Dr. Adrian Bot supporting Applicants' assertions regarding the prior art references.

Claims 1-17 and 20-29 are pending in this application. Claims 3-6 and 12-17 have been withdrawn as the result of an earlier restriction requirement without prejudice to Applicant's right to pursue the subject matter of the withdrawn claims in one or more related applications. Claims 11, 18 and 19 were previously cancelled.

Rejections Under 35 U.S.C. §103

It is well established that a *prima facie* case of obviousness requires that the Office provide evidence to support three basic criteria: there must be some suggestion or motivation in the cited references or in the art generally to modify a reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references must teach or suggest all the claim limitations. MPEP 2143.

Moreover, Office is respectfully reminded of the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or

motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993) see also *Takeda Chemical Industries, Ltd. v. Alpharma Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007).

In order for the 35 U.S.C. §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q. 2d 1529, 1531 (Fed.Cir. 1988).

Applicants submit herewith a declaration by an immunologist, Dr. Adrian Bot, to address the pending rejections over Hooper et al. and Thomson et al. The arguments below refer to this declaration.

The rejection of claims 1-2, 7-11 and 20 under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. and Thomson et al. has been maintained.

The Office asserts that Hooper teaches immunogens of at least two membrane-associated proteins in poxviruses including variola virus (page 2, paragraph 0009) and that Thomson "teaches a polyepitope protein which is a polyprotein." (Page 3, 3rd paragraph, Office Action of October 29, 2007). Applicants respectfully disagree.

Thomson neither teaches nor suggests a polyprotein. Thomson never uses the term polyprotein. Thomson does teach a polyepitope or "polytope". The Office takes the position that these terms are equivalent or at least overlapping in meaning. This assertion is incorrect and unsupportable. As explained in the attached declaration of Dr. Adrian Bot, the two terms are commonly understood by one of skill in the art to have distinct meanings and under any reasonable interpretation refer to macromolecules that are structurally and functionally distinct.

A polyepitope is a polypeptide made up of many epitopes. The Online Medical Dictionary (<http://cancerweb.ncl.ac.uk/omd/>) defines epitope as "[t]hat part of an antigenic molecule to which the T-cell receptor responds, a site on a large molecule against which an antibody will be produced and to which it will bind". While other sources will undoubtedly vary in the exact phraseology this definition sets forth key

elements of how this term is understood by one of skill in the art. Notably it points out that an epitope is only a part of an antigen, specifically that part that interacts with the immune-cell receptor, and that there are distinctions between epitopes that interact with T-cell receptors and those that interact with B-cell receptors (antibodies).

Thomson, in the abstract, describes his polyepitope as containing “multiple contiguous minimal murine CTL (Cytotoxic T Lymphocyte) epitopes”. Thomson also describes that the multiple epitopes are derived from diverse antigens. This is entirely consistent with the general understanding of the term polyepitope to one of skill in the art. This definition, along with other teachings of Thomson, confirms that the various epitopes are directly joined one to the next (contiguous), that these are T-cell receptor interacting epitopes presented by class I MHC (CTL epitopes), and that the epitopes are limited in size to only the length, generally 8-10 amino acids, that can be effectively bound by class I MHC molecules (minimal).

Thus both Thomson and persons of ordinary skill in the art are in agreement that a polyepitope is an artificial polypeptide in which multiple minimal T cell epitopes are arranged adjacent to each other in a continuous string.

A polyprotein is a macromolecule made up of at least 2 proteins. As discussed in the attached declaration, although there is not a universally accepted absolute minimum size for a protein it is equally clear that there is an accepted meaning in the field including a size limitation and that a peptide sequence substantially less than 40 amino acids does not conform to the meaning that “a protein” has to one of skill in the art. Furthermore, a protein is the translation product of a gene and possesses a particular structure. Thus the term also implies a degree of completeness.

The epitopes of Thomson’s polyepitope and the proteins of the instant application’s polyprotein are not the same, nor do they overlap. Fragments of an antigen 8-10 amino acids in length are distinctly different from complete or substantially complete antigens of at least 40 amino acids in length. Thus Thomson does not teach or suggest the polyprotein of the instant application.

Thomson explicitly teaches the use of minimal epitopes so as to maximize the number of epitopes that can be delivered by a single, relatively small DNA construct and denigrates as problematic the use of a single plasmid to express multiple proteins (see Thomson, abstract, 1st paragraph of the article, and last paragraph of the Discussion section). Thus Thomson teaches away from encoding whole or substantially whole proteins in a single vector as in the polyprotein of the instant invention.

The instant application indicates that the immunogenic compositions (and component polyproteins) should be capable of inducing an immune response including a neutralizing antibody response (see, for example, [0019], [0025], [0029], [0033], [0036-7], Examples 1, 3, 6, and 7). Antibodies, particularly neutralizing antibodies, typically recognize conformational (discontinuous) epitopes which depend on the native 3-dimensional structure of the antigen. In contrast CTL epitopes must be processed into short, necessarily continuous peptides and presented by MHC proteins in order to be recognized by the immune system. For these reasons one of skill in the art would not consider an article such as Thomson, which is directed to vectors for the generation of a CTL response, to teach anything particularly pertinent to designing vectors for the generation of an immune response including a neutralizing antibody response. Indeed such considerations show that general knowledge in the art, far from providing motivation to combine references in the manner presented in the Office Action, clearly show that one of skill in the art would be disinclined to do so. Furthermore, Thomson discloses that despite the inclusion of a known, highly immunogenic linear antibody epitope in his construct, no antibody response was obtained (paragraph bridging pp. 1719-21; last paragraph, left col. p. 1722). Thus one of skill in the art would consider that Thomson's design was not able to induce a neutralizing antibody response, that in fact it teaches away from the use of such designs for the induction of an antibody response.

The Office is respectfully reminded that if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

For these reasons, Thomson cannot be modified to produce the polyprotein of the instant application.

A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

Applicants respectfully submit that Hooper and Thomson, either singly or in combination, do not teach or suggest each and every element of claims 1-2, 7-11 and 20, namely a polyprotein comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses. Furthermore, there is no suggestion or motivation in the cited art to modify or to combine the reference teachings and there is not a reasonable expectation of success. For each of these reasons the Office has therefore not established *prima facie* obviousness of claims 1-2, 7-11 and 20 over Hooper in view of Thomson.

The rejection of claim 21 under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. in view of Thomson et al. and further in view of Curiel et al. has been maintained.

Hooper and Thomson have been discussed *supra*. The deficiencies of Hooper and Thomson as invalidating 35 U.S.C. §103(a) art are not remedied by Curiel. Curiel teaches viral conjugates wherein the virus and a nucleic acid binding domain are bound by a biotin-streptavidin bridge. Curiel does not teach or suggest a polyprotein.

Applicant respectfully submits that the cited references, in combination, do not teach or suggest each and every element of claim 21, there is no suggestion or motivation in the cited art to modify or to combine the reference teachings and there is

not a reasonable expectation of success. Therefore the Office has not established *prima facie* obviousness of claim 21 over Hooper in view of Thomson and Curiel.

The rejection of claim 22 under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. in view of Thomson et al. and further in view of Rutter et al. has been maintained.

Hooper and Thomson have been discussed *supra*. The deficiencies of Hooper and Thomson as invalidating 35 U.S.C. §103(a) art are not remedied by Rutter. Rutter teaches agents to facilitate the delivery of a viral subunit vaccine wherein the agent is a liposome. Rutter does not teach or suggest a polyprotein.

Applicant respectfully submits that the cited references, in combination, do not teach or suggest each and every element of claim 22, there is no suggestion or motivation in the cited art to modify or to combine the reference teachings and there is not a reasonable expectation of success. Therefore the Office has not established *prima facie* obviousness of claim 22 over Hooper in view of Thomson and Rutter.

The rejection of claims 23-29 under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. in view of Thomson et al. and further in view of Newton et al. has been maintained for claims 23-29 and further for claims 30-31.

Hooper and Thomson have been discussed *supra*. The deficiencies of Hooper and Thomson as invalidating 35 U.S.C. §103(a) art are not remedied by Newton. Newton teaches linkers to link peptides wherein the linkers include a (GGGGS)₃ linker. Newton also teaches affinity tags. Newton does not teach or suggest a polyprotein.

Applicant respectfully submits that the cited references, in combination, do not teach or suggest each and every element of claims 23-31, there is no suggestion or motivation in the cited art to modify or to combine the reference teachings and there is not a reasonable expectation of success. Therefore the Office has not established *prima facie* obviousness of claims 23-31 over Hooper in view of Thomson and Newton.

Conclusion

Applicants respectfully assert that the presently pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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